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BRIEF ARTICLES

Portal hypertension secondary to myelofibrosis with myeloid metaplasia: A study of 13 cases

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Abstract

AIM: To describe the clinical presentation and complications of portal hypertension (PH) secondary to myelofibrosis with myeloid metaplasia (MMM).

METHODS: Medical records for 123 patients with MMM were reviewed.

RESULTS: Thirteen patients with PH secondary to MMM were identified. Median ages at time of MMM and PH diagnosis were 61 and 66 years, respectively. The interval from MMM diagnosis to presentation with one of the PH features ranged from 1 to 11 years. Variceal bleeding and ascites were the most common presentations. Of the eight patients who presented with variceal bleeding, six patients underwent endoscopic variceal ligation (EVL) with no variceal recurrence or hematological worsening during a 12-mo follow up period.

CONCLUSION: Patients with MMM might develop PH. Exact mechanisms leading to PH in MMM are still controversial. As in other etiologies, variceal bleeding and ascites are the most common presentations. Anemia may correlate with, and/or predict, the severity of the PH presentation in these patients. EVL can successfully control variceal bleeding in MMM. Further clinical studies are required.

Key words: Portal hypertension; Myelofibrosis; Myeloid metaplasia; Ascites; Variceal bleeding

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INTRODUCTION

The term "myelofibrosis with myeloid metaplasia (MMM)" is usually referred to for patients with chronic idiopathic myelofibrosis (CIM), also known as angiogenic myeloid metaplasia (AMM), and for those with advanced phases of polycythemia vera [post polycythemic myeloid metaplasia (PPMM)] and essential thrombocythemia [post thrombocythemic myeloid metaplasia (PTMM)]. All three represent chronic stem cell-derived clonal myeloproliferative diseases that, in the case of myeloid metaplasia, are accompanied by an intense reactive bone marrow fibrosis that leads to ineffective erythropoiesis and extramedullary hematopoiesis in multiple organs, predominantly the spleen. However, extramedullary hematopoiesis may also occur at sites other than the spleen, including lymph nodes causing lymphadenopathy and also in the liver resulting in hepatomegaly and possibly, with other contributing factors, portal hypertension (PH)[1,2].

Patients with MMM present with variable clinical and histomorphologic features. The typical clinical features include hypermetabolic symptoms (fever, fatigue and weight loss), marked splenomegaly and anemia[3]. PH with subsequent ascites and gastrointestinal hemorrhage from ruptured varices has been described in patients with MMM[4-8]. Only a few published studies have discussed this issue extensively. Furthermore, these reports described and focused on PH in CIM which represents a subgroup of MMM. In this retrospective study, we describe 13 patients with PH secondary to MMM.

MATERIALS AND METHODS

After obtaining approval from the Institutional Review Board of our institution, the study patients were identified through the use of a comprehensive institutional database of medical diagnoses and procedures. Between January 1, 1995 and December 31, 2007, an estimated number of 123 patients with MMM were evaluated at the Mayo Clinic, Rochester, MN. The diagnosis of MMM was confirmed on the basis of traditional criteria that included bone marrow fibrosis associated with splenomegaly and leukoerythroblastosis (immature granulocytes and nucleated red cells). Patients with bone marrow fibrosis resulting from other disorders were excluded. This included patients with myelodysplastic syndrome, acute myelofibrosis, or chronic myelogenous leukemia.

From this sample, a subgroup of 13 patients with clinical evidence of PH was identified. Although the gradient between wedged and free hepatic venous pressure was not assessed in many patients, the diagnosis of PH was based on clinical criteria [e.g. esophageal varices by endoscopy, ascites with Serum-Ascites Albumin Gradient (SAAG) > 1.1] in conjunction with imaging studies. Patients with liver disease and patients having risk factors for liver disease such as chronic alcohol consumption were excluded. Patients with PH due to other diseases were also excluded. The medical records for these 13 patients with PH secondary to MMM were comprehensively reviewed. Pertinent clinical and laboratory variables were recorded for all patients.

Table 1 Clinical characteristics, presentation and laboratory values within 1 wk of PH diagnosis for the 13 patients

Variable	
Age (yr), median (range)	
All patients	67 (49-88)
At time of diagnosis of MMM	61 (45-79)
At time of diagnosis of PH	66 (47-84)
Interval till presentation with PH	5 (1-11)
Sex *n* (%)	
Male	9 (69)
Female	4 (31)
Type of MMM *n* (%)	
AMM	6 (46)
PPMM	6 (46)
PETMM	1 (8)
Initial presentation *n* (%)	
GI bleeding only	3 (23)
Ascites only	3 (23)
GI bleeding and ascites concurrently	2 (15)
Jaundice (with GI bleeding)	1 (8)
Encephalopathy	0 (0)
Abdominal pain (with ascites)	1 (8)
Splenomegaly	13 (100)
Hepatomegaly	9 (69)
Portal vein thrombosis	3 (23)
CBC, median (range)	
Hemoglobin (g/dL)	10 (6.6-13.9)
WBC ($\times 10^9$/L)	8.8 (2.1-49)
Platelet count ($\times 10^9$/L)	225 (47-694)
Liver function, median (range)	
AST (U/L)	69 (26-172)
Alkaline phosphatase (U/L)	338 (74-850)
Total bilirubin (mg/dL)	0.9 (0.3-2.2)
PT (s)	12.4 (10.8-14.1)
Albumin (g/dL)	4 (2.8-4.4)
SAAG	2 (1.9-2.4)

PT: Prothrombin time.

RESULTS

Thirteen patients with PH secondary to MMM were identified. Table 1 shows their pertinent clinical characteristics, presentation and laboratory values within 1 wk of PH diagnosis. Nine male (69%) and four female patients (31%) were identified: six patients (46%) had AMM, six patients (46%) had PPMM, and one patient (8%) had PTMM. The age of the patients ranged from 49 to 88 years (median, 67 years). Median ages and range at time of MMM and PH diagnoses were 61 (45-79) years and 66 (47-84) years respectively. The interval from MMM diagnosis to presentation with one of the PH features ranged from 1 to 11 years (median, 5 years).

Variceal bleeding and ascites were the most common presentations. Six patients (46%) initially presented with GI bleeding (five patients presented with acute upper GI bleeding and one presented with melena). Among those six patients; three presented with GI bleeding only, two presented with both GI bleeding and ascites, and one presented with GI bleeding and jaundice. All the six patients were diagnosed as having mild to moderate esophageal varices (Grade 1 to 2). Five patients (38%) presented initially with ascites. Among these five patients; three had only ascites at presentation, two presented with GI bleeding with the ascites, and one patient presented with abdominal pain in addition to ascites. SAAG was calculated in patients with ascites; all had SAAG above 1.1 which was considered as indicative of PH. Amongst all 13 patients, 12 of them (92%) eventually developed at least one episode of ascites within 6 mo from initial presentation. Jaundice was never the sole presenting feature. One patient presented with jaundice in addition to GI bleeding. Another patient developed jaundice afterwards, during the course of the disease. None presented with encephalopathy.

All patients (100%) had splenomegaly; nine patients (69%) had hepatomegaly and consequently nine patients (69%) had both. Eleven patients (84%) had elevated alkaline phosphatase levels at time of PH diagnosis, nine patients (69%) had elevated aspartate aminotransferase levels, and eight patients (62%) had both enzyme levels elevated. Median and range values for all liver tests are displayed in Table 1. Hyperbilirubinemia was present in four patients (31%) at time of PH diagnosis but jaundice was uncommon. Four patients (31%) had low albumin, with a median albumin level of 4 g/dL (2.8-4.4 g/dL). Ten patients (77%) were anemic at the time of PH diagnosis. Median hemoglobin level was 10 mg/dL (6.6-13.9 mg/dL). Three patients (23%) were diagnosed with portal vein thrombosis at time of

PH diagnosis, indicated by either abdominal doppler ultrasound (US) or CT or MRI. Among these three patients with portal vein thrombosis, one patient had high white blood cell count and low hemoglobin, while the other two patients had white blood counts and hemoglobin levels within normal limits but had decreased portal blood flow velocity indicated by abdominal doppler US. Among the 10 patients who did not have thrombosis, eight patients have undergone liver biopsy: all eight showed non cirrhotic liver parenchyma with varying degrees of extramedullary hematopoiesis, and infiltration of liver sinusoids with hematopoietic cells (myeloid metaplasia). Two of these eight patients also had mild fibrotic changes but none of them had truly cirrhotic features. All patients, including those without thrombotic etiology, had splenomegaly. Of the eight patients presenting with variceal bleeding, six patients underwent endoscopic variceal ligation (EVL) requiring 1-4 sessions. These six patients were followed up by endoscopies at 1, 3 and 12 mo to inspect for the re-appearance of varices. Varices were completely obliterated with no recurrence at the 12 mo time point. No hematologic worsening was recorded during the 12 mo follow-up period. The other two patients underwent endoscopic variceal sclerotherapy (EVS) but were not followed up. Interestingly, three patients (23%) had pulmonary hypertension concurrent with PH, with no cardiopulmonary causes.

DISCUSSION

PH has been reported in 7%-18% of AMM, which represents a subgroup of MMM[8,9]. In this study, simple mathematical calculation revealed an 11% prevalence of symptomatic PH in MMM. However, as in other most etiologies, PH secondary to MMM is usually asymptomatic and diagnosis of PH in these patients is often not made until they become symptomatic, which sometimes does not become apparent for up to 11 years. In the present study we found that the median interval for our patients to present with one of the PH features is 5 years, ranging from 1-11 years. Taking into consideration that the median survival for patients with MMM is 4 years[10-15], this suggests that many MMM patients die due to the underlying disease before they become symptomatic from PH. Therefore, we believe that a prevalence of 11% represents the prevalence of symptomatic PH and that the true prevalence of PH in MMM, including the asymptomatic PH, is higher.

When patients become symptomatic, they usually present either with acute upper GI bleeding from ruptured varices or in the form of melena, or they present with ascites. Other presentations such as jaundice and encephalopathy are unlikely.

Exact mechanisms leading to PH in MMM are still controversial. In the absence of portal and/or hepatic vein thromboses two theories have been proposed. The first theory states that PH develops in MMM patients due to sinusoidal narrowing and intrahepatic obstruction caused by extramedullary hematopoiesis and infiltration of the liver by myeloid cells leading to increased intrahepatic resistance[6,16,17], while the other theory states that PH develops in such patients due to increased portal blood flow through the enlarged spleen[8,18,19].

Portal vein thrombosis is a major cause of PH in hematological disorders[6,16,18]. It is still unclear whether portal vein thrombosis in MMM is caused by a hypercoagulable state and hyperviscosity related to underlying disease or as a consequence of stasis due to elevated sinusoidal pressure. In our study, PH in three of our patients (23%) was due to thrombosis of the portal and/or hepatic veins as indicated by imaging studies. The three patients had prothrombin time within normal limits. However, one of these patients had a very high white blood cell count (49 000 cells/mL), possibly contributing to thrombosis by increasing the blood viscosity. When thrombosis is absent, PH has been related to an increased intrahepatic resistance and sinusoidal narrowing due to the myeloid metaplasia[6,16,17] and/or due to a marked increase in portal flow as a consequence of marked splenomegaly[8,18,19]. In our report, the 10 patients who did not have portal vein thrombosis had splenomegaly; six of them had dilated splenic veins with increased portal blood flow indicated by abdominal doppler ultrasound. The increase in portal flow itself may explain PH. In fact, few cases of PH in myelofibrosis patients secondary to increased splenic and/or portal flow with minimal hematopoiesis have been reported[20,21]. On the other hand, Sikuler *et al*[22] experimentally demonstrated that in the absence of structural alteration of the liver, PH does not develop as a consequence of an increased portal flow. They proposed that the main contributory factor is the increased intrahepatic resistance caused by obstruction due to extramedullary hematopoiesis of the liver. In our group of patients, liver biopsy in those six patients with increased portal flow and another two patients without increased portal flow showed infiltration of liver sinusoids with hematopoietic cells and myeloid metaplasia. Therefore six of our patients, without thrombotic etiology, have both enhanced portal flow and increased intrahepatic resistance as contributing factors. Hence, it seems that in absence of thrombosis, both enhanced portal flow from the enlarged spleen and intra-hepatic sinusoidal obstruction have synergistic effects, so that even a slight increase in resistance in the face of enhanced portal flow might produce clinically significant PH.

Patients with PH characteristically exhibit a hyperdynamic circulation with increased cardiac output and decreased peripheral resistance[23]. Overactivity of some vasodilator factors has been proposed and there is a growing body of evidence suggesting that endogenous NO accounts for much of this activity[24-26]. Anemia, which is a very common feature in patients with MMM, has been shown to further worsen the hyperdynamic circulation associated with PH[27-29]. In this group of patients, 10 patients (77%) were anemic at the time of PH

diagnosis. At presentation, a total of four patients had a picture of severe PH. Three of these four patients had profound anemia (hemoglobin 6.6, 6.9 and 7.1 mg/dL) suggesting that anemia, possibly by worsening the hyperdynamic circulation, might have a role in exacerbating PH and that anemia may correlate with and/or predict the severity of the PH presentation in these patients. Experimental studies have demonstrated that increasing blood hemoglobin levels partially correct PH hyperdynamic circulation in rats[30]. However, clinical data focusing on the role of anemia on the hyperdynamic state are scant and more studies are needed.

The optimal management of PH secondary to MMM and management of subsequent variceal hemorrhage and ascites have not been well established. Based on the theory of increased portal flow due to splenomegaly as a mechanism for the PH in MMM patients, splenectomy would be a reasonable choice. In fact, splenectomy, which is commonly performed for patients to relieve abdominal discomfort and early satiety caused by the mass effect of the enlarged spleen, has effectively reversed PH in selected patients[4,31]. However, increased blood flow from an enlarged spleen is not the sole mechanism for development of PH in MMM patients. Also, the enlarged spleen may possibly be the main or even the only site for red cell production in patients with advanced MMM. Moreover, there are some unique post-operative complications such as massive hepatomegaly due to extramedullary hematopoiesis in 16%-24% of splenectomized MMM patients leading to liver failure in some cases, post-splenectomy extreme thrombocytosis in up to 50% of splenectomized MMM patients, and the major concern of leukemic transformation. All these factors, together with the knowledge that splenectomy has not been shown to improve overall survival in MMM patients, must be strongly considered before proceeding for splenectomy to manage PH[3,32-34].

PH caused by intra-hepatic or portal obstruction requires interventional or surgical portosystemic shunting. Relief of intra-hepatic PH in patients with MMM can be accomplished by implantation of a transjugular intrahepatic portosystemic shunt (TIPS)[35-37]. TIPS is an effective and well established procedure that involves creation of a side-to-side portocaval shunt in the liver and it has very good efficacy for intractable ascites. However, such a procedure needs ideal candidates who display normal liver synthetic function with little interventional risk. Only a few reports have been published regarding the use of TIPS for PH secondary to MMM, but these have proved to be effective[3,35-39]. Few data exist regarding the outcomes of this procedure in MMM patients and more studies are needed to examine whether it prolongs survival or just alleviates variceal hemorrhage and recurrent ascites.

Managing the acute bleeding episodes consists of general resuscitative measures such as volume and blood replacement, and specific measures to stop bleeding. EVL[40-42] as well as EVS[7] have been utilized successfully for the management of GI bleeding in MMM patients. EVL has been reported to have very good efficacy, with fewer therapeutic sessions and complications when compared to EVS in variceal bleeding due to other etiologies[43]. In our report, six out of eight patients who had variceal bleeding underwent EVL with no variceal recurrence or hematological worsening during a brief 12 mo follow up period. Nevertheless, there is a paucity of data regarding the use of EVL in patients with MMM-associated PH and further studies are required. We report our successful experience with EVL in this small group of patients.

In conclusion, patients with MMM might develop PH. Exact mechanisms leading to PH in MMM are still controversial. In the absence of portal vein thrombosis, both increased intrahepatic resistance due to sinusoidal narrowing caused by extramedullary hematopoiesis and a rise in portal pressure, *via* an increase in portal blood flow secondary to increased splenic blood flow from an enlarged spleen, might play a role in the pathogenesis of PH. Clinical presentation is similar to PH due to other etiologies with variceal bleeding and ascites being the most common presentations. Anemia may correlate with, and/or predict the severity of, the PH presentation in these patients. EVL can successfully control variceal bleeding in MMM. Further clinical studies are required.

COMMENTS

Background

Patients with myelofibrosis with myeloid metaplasia (MMM) present with variable clinical features. The typical clinical features include constitutional symptoms, splenomegaly and progressive anemia. Portal hypertension (PH) with subsequent variceal bleeding and ascites has been described.

Research frontiers

Few published studies have discussed PH in patients with MMM. However, these small reports described and focused on PH in chronic idiopathic myelofibrosis (CIM) which represents a subgroup of MMM.

Innovations and breakthroughs

In this retrospective study, the authors describe clinical presentation and complications of 13 patients with PH secondary to MMM. The article also discusses the possible mechanisms leading to PH in these patients and the possible treatment options.

Applications

Patients with MMM might develop PH. As in other etiologies, variceal bleeding and ascites are the most common presentations. Exact mechanisms leading to PH in MMM are still controversial. Interestingly, anemia may correlate with and/or predict the severity of the PH presentation in those patients. Endoscopic variceal ligation can successfully control variceal bleeding in these patients. However, further clinical studies and trials are required.

Terminology

PH is an increase in the pressure within the portal vein and its tributaries. It is defined as a portal pressure of 12 mmHg or more compared with a normal figure of 5-8 mmHg. Myelofibrosis with myeloid metaplasia is a term referred to for patients with CIM, also known as angiogenic myeloid metaplasia, and advanced phases of polycythemia vera and essential thrombocythemia.

Peer review

This is a retrospective study of patients with myelofibrosis and PH. The authors describe the clinical presentation and complications of this unusual condition. The paper is well written and includes a discussion of the pathogenesis of PH in myelofibrosis.

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